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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/706,328 | 11/12/2003 | Alison Hannah | 072121-0366 | 6441 |

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NOVARTIS VACCINES AND DIAGNOSTICS INC.
CORPORATE INTELLECTUAL PROPERTY R338
P.O. BOX 8097
Emeryville, CA 94662-8097

| EXAMINER | |
|---|---|
| ANDERSON, JAMES D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/706,328 | HANNAH ET AL. | |
| | Examiner | Art Unit | |
| | James D. Anderson | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38 and 49-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38 and 49-64* is/are rejected.

7)☒ Claim(s) *51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' arguments, filed 8/17/2006, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. In light of the new rejections being applied against the pending claims, this Office Action is Non-Final.

### *Status of the Claims*

Claims 1-38 and 49-64 are currently pending and are the subject of this Office Action. Claims 1, 9, 36, 49, 52 and 53 are currently amended and claims 59-64 are newly presented. Applicants cancelled claims 39-48, without prejudice, in the reply filed 8/17/2006.

### *Priority*

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application Nos. 60/426,107; 60/426,282; 60/426,226; 60/426,204; 60/460,328; 60/460,493; 60/460,327; 60/460,369; and 60/478,916, fail

to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application. The cited U.S. Provisional Applications fail to provide adequate support for the instantly claimed limitations of $C_{max}$ and dose ranges. Support for the instantly claimed invention was found in U.S. Provisional Application No. 60/517,915, filed 11/7/2003 (see especially Claims).

As such, the earliest effective U.S. filing date of the instantly claimed invention has been determined to be November 7, 2003.

***Information Disclosure Statement***

Examiner has considered he information disclosure statement (IDS) submitted on 8/17/2006 to the extent that the references disclosed therein are proper citations. Please see attached Form 1449.

***Claim Objections***

Claim 51 is objected to under 37 CFR § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 51 depends from claim 50, which depends from claim 49. As such, claim 51 carries forth all of the limitations of claims 49 and 50. Claim 49 requires that the amount of compounds administered is increased with each subsequent treatment cycle and claim 50 requires that the amount of the compound is doubled with each subsequent treatment cycle. However, claim 51 comprises administering the same amount of the

compound daily for 7 days. Thus, claim 51 does not further limit claims 49 and 50 from which it depends.

***Claim Rejections - 35 USC § 112 – First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 and 49-64 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

In the instant case, claims 1, 9, 49, 52, and 53 were amended to recite the limitation wherein the cancer being treated "comprises cells expressing a receptor tyrosine kinase". Applicants state that paragraphs 81-82 provide support for the introduced limitation. However, examiner notes that paragraphs 81-82 are drawn to effective amounts of the claimed compounds, not limitations with respect to the treatment group. For example, paragraph 81 states that effective amounts of the compounds include those amounts that inhibit RTK. There is no disclosure in the claims or specification as originally filed that applicants only intended to treat or contemplated treating only cancers wherein the cancer cells express a receptor tyrosine kinase.

Claims 1-24, 28-38 and 49-64 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of KM1412a tumors in mice and determination of $C_{max}$ in mice administered with the specific doses disclosed Table 5 (page 48), does not reasonably provide enablement for the treatment of any and all cancers with amounts of the claimed compound "to provide" the claimed $C_{max}$ (*e.g.* claim 1), plasma concentrations (*e.g.* claim 9), and AUC (*e.g.* claim 36). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are missing an essential step, critical to the practice of the claimed invention. Namely, the instant claims do not recite the measurement of a $C_{max}$, plasma drug concentration, or AUC. As such, it is not clear how one skilled in the art would know when an appropriate dosage is being administered. While the specification recites a protocol for administering and determining the $C_{max}$ and plasma concentrations of the drug in mice carrying a KM1412a tumor, there is no direction or guidance to determine similar parameters in any other subjects with any other cancer.

The pharmacokinetics of any particular drug is dependent on several factors. For example, a subject's metabolism, weight, sex, and condition will all affect the $C_{max}$ and plasma concentration of an administered drug. Further, the dose, route of administration, frequency of dosing, and metabolism of the drug will also have an effect on the $C_{max}$ and plasma concentration of a particular drug. In the instant case, neither the claims nor the specification recite any particular dosages, routes of administration, frequency of administration, etc. necessary to treat any and all cancers. Further, there is no disclosure of how one skilled in the art would administer

the instantly claimed drug (*e.g.* dose, route, frequency, etc.) to achieve the claimed $C_{max}$, plasma concentration, and AUC ranges in any subject other than a mouse. It is well known in the art that the aforementioned pharmacokinetic parameters differ among various species of mammal and also differ depending on the dose, frequency of administration, route of administration, metabolism of the drug, among many other parameters.

Thus, it would take undue experimentation on the part of the skilled artisan to practice the claimed invention. Specifically, the skilled artisan would have to determine, with no guidance from the instant specification, the appropriate dose, route of administration, and frequency of administration required to both treat each particular cancer as well as determine the $C_{max}$, plasma concentration, and AUC for each particular administration regime. All of these experiments would have to be repeated for each type of subject to be treated (*e.g.* human, monkey, rat, dog, etc.) and for each type of cancer being treated.

***Claim Rejections - 35 USC § 112 – Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites the limitation "further comprising mixing the solid compound..." in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claims 1-38, 52-61 and 63-64 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a measurement of $C_{max}$, AUC, or plasma concentration following administration of the claimed compound. Claims 1, 9, 36, 52, and 53 recite limitations wherein an amount of compound is administered so as to provide specific ranges of $C_{max}$, AUC, or plasma concentration. However, the claims do not recite any step wherein a determination of $C_{max}$, AUC, or plasma concentration is made after administration of a dose of the compound. As such, it is not clear how one skilled in the art would practice the claimed invention without actually measuring the $C_{max}$, AUC, or plasma concentration following administration of the compound to a subject.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR § 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR § 3.73(b).

Claims 1-7, 9-12, 14, 25-30, 36-38, and 52-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38, 40, and 49-52 of copending Application No. 10/116,117. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claims of the '117 application and the instant application are drawn to the treatment of cancer wherein the cancer cells express a receptor tyrosine kinase comprising administration of the same compound. The claims differ in that the instant claims recite specific limitations with respect to $C_{max}$ and AUC. However, these limitations are an inherent property of the claimed compound when administered to a subject. As such, practice of methods of the '117 application would naturally result in the $C_{max}$ and AUC ranges as recited in the instant claims (*i.e.* administering the same compound to a subject to treat cancer would inherently result in the instantly claimed $C_{max}$ and AUC ranges). It is noted that the claims of the '117 application are extremely broad and do not recite a specific dose. As such, the claims read on the administration of <u>any</u> dose of the claimed compound to treat cancer. Naturally, there is at least one dose encompassed by the '117 claims that will result in the $C_{max}$ and AUC ranges instantly claimed.

This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-7, 9-12, 14, 25-30, 36-38, and 52-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 16 and 17 of copending Application No. 10/886,950. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '950 application are drawn to the treatment of a patient in need of an inhibitor of a receptor tyrosine kinase (claim 13) and wherein the patient is a cancer patient (claim 17) and the instant application are drawn to the treatment of cancer wherein the cancer cells express a receptor tyrosine kinase comprising administration of the same compound. The claims differ in that the instant claims recite specific limitations with respect to $C_{max}$ and AUC. However, these limitations are an inherent property of the claimed compound when administered to a subject. As such, practice of methods of the '950 application would naturally result in the $C_{max}$ and AUC ranges as recited in the instant claims (*i.e.* administering the same compound to a subject to treat cancer would inherently result in the instantly claimed $C_{max}$ and AUC ranges). It is noted that the claims of the '950 application are extremely broad, encompassing the administration of the claimed compound in any dose to treat cancer. Naturally, there is at least one dose encompassed by the '950 claims that will result in the $C_{max}$ and AUC ranges instantly claimed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-14, 25-30, 36-38, and 52-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7-8, 10-

17, 19-20 and 22 of copending Application No. 11/342,257. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '257 application are drawn to the treatment of a subject having a metastasized tumor (*i.e.* cancer) and the claims of the instant application are drawn to the treatment of cancer wherein the cancer cells express a receptor tyrosine kinase. The conflicting claims both comprise administration of the same compound. The claims differ in that the instant claims recite specific limitations with respect to $C_{max}$ and AUC. However, these limitations are an inherent property of the claimed compound when administered to a subject. As such, practice of methods of the '257 application would naturally result in the $C_{max}$ and AUC ranges as recited in the instant claims (*i.e.* administering the same compound to a subject to treat cancer would inherently result in the instantly claimed $C_{max}$ and AUC ranges). It is noted that the claims of the '257 application do not recite a specific dose. As such, the claims read on the administration of <u>any</u> dose of the claimed compound to treat cancer. Naturally, there is at least one dose encompassed by the '257 claims that will result in the $C_{max}$ and AUC ranges instantly claimed.

This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-38 and 49-64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 6,605,617. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 30 of the '617 recites a method of treating a patient in need of an inhibitor of VEGF receptor tyrosine kinase comprising administering a compound according to anyone of claims 1,

8, 15 or 22. The genus of compounds recited in the claims of the '617 patent include the instantly claimed compound. Further, the specification of '617 specifically recites the claimed compound (col. 86, Example 109) and further states that the disclosed compounds can be used to inhibit tumor growth (col. 61, lines 11-14). Thus, it would have been *prima facie* obvious to use the compounds disclosed in the '617 patent, including the instantly claimed compound, in a method to treat a cancer expressing VEGF. Further, because claim 30 of '617 is so broad so as to include administration of any amount of the claimed compounds to treat a VEGF mediated disease (including tumors), the claim reads on the instantly claimed ranges of $C_{max}$, AUC, and plasma concentrations of the instantly claimed compound.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

October 26, 2006

Ardin H. Marschel 10/29/06

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER